

REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-27 are pending. Claims 17-27 were examined on the merits. Although nonelected claims 1-16 were withdrawn from consideration by the Examiner, Applicants request their rejoinder upon an indication that an elected product claim is allowable.

The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. Support may be found, *inter alia*, at page 17, lines 20-31, of the specification. Entry of the amendments will reduce the issues on appeal.

Information Disclosure Statement

To satisfy their continuing duties of candor and good faith, Applicants bring to the attention of the Examiner the related subject matter in Application Nos. 09/738,879, 09/950,003, 10/240,606, 10/274,706, 10/484,883, 10/496,037, 10/518,229, 10/518,302, 10/518,303, 10/868,359, 10/902,285, 11/030,156, 11/440,749, 12/120,167, 12/198,426 and the two documents.

The Examiner is invited to consider their prosecution histories and the prior art of record in those applications, which are accessible through Image File Wrapper (IFW), in view of the Court's holding in *McKesson Information Solutions v. Bridge Medical*, 82 USPQ2d 1865 (Fed. Cir. 2007). To avoid duplication of those materials in the PTO's records, reference to the IFW is encouraged but Applicants would be ready to submit copies of these materials for the Examiner's review if she prefers.

Form PTO-1449 listing documents for the Examiner's consideration is attached. No fee is due because this Information Disclosure Statement is being submitted with a Request for Continued Examination (RCE). As provided by 37 CFR §§ 1.97(g) and (h), no representation is being made that a search was conducted or that this statement encompasses all possible material information. Furthermore, no inference should be made that the cited documents are prior art merely because they are submitted for consideration. Consideration of the listed documents and the Examiner's return of a copy of the Form PTO-1449 with her initials per M.P.E.P. § 609, are earnestly solicited.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See *id.* (“Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue”). The use of hindsight reasoning is impermissible. See *id.* at 1397 (“A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning”). Thus, a *prima facie* case under Section 103(a) requires “some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct.” *Kahn* at 1335; see *KSR* at 1396. An inquiry is required as to “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *Id.* at 1396. But a claim that is directed to a combination of prior art elements “is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *Id.* Finally, a determination of *prima facie* obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 17-21, 23-25 and 27 were rejected under Section 103(a) as allegedly unpatentable over Oreste et al. (WO 02/50125). Applicants traverse the Examiner’s allegation of *prima facie* obviousness because the degree of sulfation from 2.3 to 2.9 does not correlate with the claimed product’s low antithrombin activity. Instead, it is the sulfation of glucosamine units (glucosamine-3-O-sulfate or A-3-OS groups) according to claim 17 that provides a depolymerized-LMW-epiK5-N,O-sulfate having anti-Xa and anti-IIa activities that are not more than 50% of low molecular weight heparin. See page

9, lines 8-9, and page 25, lines 10-12, of the specification. This effect was unexpected from the prior art and demonstrates the nonobviousness of the claimed invention.

The present amendments clarify the differences between the synthetic process used in this application and WO 02/50125. Support may be found, *inter alia*, at page 17, lines 20-31, of Applicants' specification that teaches base treatment of a depolymerized-LMW-epiK5-N-sulfate, isolation of its organic base salt, treatment with an O-sulfation agent, and isolation of the depolymerized-LMW-epiK5-amine-O-versulfate. Thus, modification of a well-known oversulfation process in accordance with the present claim 17 (i.e., maintaining the pH at about 7 for 30 minutes to one hour) instead of isolating the salt as soon as pH 7 is reached produces a spectacular result: i.e., introduction of a large number of sulfate groups onto the otherwise very resistant 3-OH group of the glucosamine subunits.

The attached Rule 132 Declaration of Dr. Oreste supports the nonobviousness of the claimed product over the prior art. Therein it is demonstrated that a LMW-epiK5-N,O-sulfate satisfying the requirements of the present claim 17 (in particular, a sulfation degree close to the lower limit of the recited range) has the same unexpected properties as those of the product made in Example 1 of this application. The products disclosed in WO 02/50125 did not have these unexpected properties. Using the prior art processes, it would have required undue experimentation to prepare epiK5 oversulfated products having more than 25% sulfate groups on the 3-OH of the glucosamine subunits. Therefore, products made by the process required by the present claims 1 and 17 would not have been made by an obvious modification of the process disclosed in WO 02/50125.

Applicants' claimed invention requires reaction conditions that result in a high number of A-3-OS groups, much higher than achieved with the process disclosed in WO 02/50125, and having a different antithrombotic profile than the products disclosed in WO 02/50125 in respect of their ratio of anti-Xa activity to anti-IIa activity. The latter result was totally unexpected because it was not obvious that increasing the number of A-3-OS groups would provide products having an antithrombotic profile similar to low molecular weight heparin (LMWH). In hindsight, this remarkable discovery might be explained by the function of 3-O-sulfate. The attached review by Petitou et al. (*Nature*

350 suppl.:30-33, 1991) describes the total synthesis of the pentasaccharide that binds to antithrombin III (ATIII). Heparin preparations with an increased ratio of anti-Xa/anti-IIa are more effective antithrombotic agents (see last two paragraphs in the right column of page 30 concerning LMWH). The role of the 3-O-sulfate in the central glucosamine of the pentasaccharide is also remarkable because its removal completely abolishes ATIII binding (see last line of page 31 and the three first lines of page 33). Thus, it is possible that the high content of A-3-OS groups in Applicants' claimed products gives the K5 polysaccharide derivatives of the present invention an anti-Xa/anti-IIa ratio similar to that of LMWH, albeit they are structurally different.

Therefore, obvious modifications of WO 02/50125 would not result in Applicants' invention as represented by independent claim 17. Moreover, claims depending from this claim are also not rendered obvious by the cited document because all limitations of the independent claim are incorporated in its dependent claims. M.P.E.P. § 2143.03 citing *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. If the Examiner is not persuaded to allow the present claims, a telephone interview with the undersigned is requested to discuss outstanding issues.

Respectfully submitted,

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